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Neuro-Ophthalmology Update

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Disclosure

The authors declare no conflict of interest.

Abstract

This review summarizes the most relevant articles from the field of neuro-ophthalmology published in the *Journal of Neurology* from January 2012 to July 2013. With the advent of video-oculography, several articles describe new applications for eye movement recordings as a diagnostic tool for a wide range of disorders. In myasthenia gravis, anti-Kv1.4 and anti-Lrp4 have been characterized as promising novel autoantibodies for the diagnosis of hitherto ‘seronegative’ myasthenia gravis. Several articles address new diagnostic and therapeutic approaches to neuromyelitis optica (NMO), which further sharpen its profile as a distinct entity. 4-aminopyridine has become a standard therapeutic for patients with cerebellar downbeat nystagmus. Finally, revised diagnostic criteria have been proposed for chronic relapsing inflammatory optic neuropathy (CRION) based on a careful literature review over the last decade.

Keywords

Neuro-ophthalmology, eye movements, ocular myasthenia gravis, optic neuritis, neuromyelitis optica (NMO), chronic relapsing inflammatory optic neuropathy (CRION), cerebellar downbeat nystagmus, 4-aminopyridine.

Introduction

The eclectic field of neuro-ophthalmology keeps evolving rapidly. In this article we are summarizing the most relevant publications in the field published in the *Journal of Neurology* from January 2012 to July 2013. The review is divided into sections about the use of eye movement measurements as a probe of disease, novel autoantibodies for the diagnosis of myasthenia gravis, neuromyelitis optica (NMO) and chronic relapsing inflammatory optic neuropathy (CRION) and the therapeutic use of 4-aminopyridine.

Eye movements as a probe of disease

The examination of eye movements is a rich source of clinical information to neuro-ophthalmologists [1]. Thanks to detailed knowledge of the underlying neurophysiological circuits in the brainstem, eye movements provide precise information about the localization of disease and often valuable clues about its etiology. With the advent of video-oculography, the quantitative analysis of eye movements now becomes readily accessible to clinics.

Tseng et al. devised a universally applicable patient screening tool based on automated analysis of natural viewing eye movements [2]. The participants simply had to watch television while their eye movements were recorded with a head-mounted video-based eye tracker. The eye movements were then analyzed for ocular motor features such as saccade metrics, as well as visual attention based on saliency maps. The investigators analyzed patient populations from two different age groups: elderly people with Parkinson's disease as well as children with attention deficit hyperactivity disorder (ADHD) and fetal alcohol spectrum disorder (FASD). Based on eye movement recordings from only 15 min of video, the method was able to distinguish patients with Parkinson's from age-matched controls with an accuracy of 89.6 % and ADHD versus FASD children with 77.3% accuracy. While in Parkinson's the distinction was made based on ocular motor features, ADHD and FASD children were distinguished based on visual attention features. The patient-friendly nature of this automated test makes it a promising screening tool for large populations.

In a population-based incidence cohort, Linder et al. looked at eye movements in patients with newly diagnosed Parkinson syndrome before treatment [3]. They examined 105 patients with Parkinson's disease, 11 patients with progressive supranuclear palsy (PSP) and 19 patients with multiple system atrophy with predominant Parkinsonism (MSA-P). The diagnosis was established by a movement disorder specialist and supported by single-photon emission computed tomography (FP-CIT SPECT). Analysis of square-wave jerks, horizontal and vertical saccades and smooth pursuit revealed pathological ocular motor function in all patient groups. The ocular motor testing, however, could not reliably differentiate different subtypes of Parkinson syndrome early in the course of the disease. Nevertheless, some features, such as slow vertical saccade velocity or low smooth pursuit gain, were found to be indicative of PSP.

Ong and colleagues developed *Read-Right*, a free web-based application (see www.readright.ucl.ac.uk) to improve reading in patients with right-sided hemianopia [4]. First, the web application automatically assessed the visual field of the patients. Then reading speed was measured with six standardized paragraphs of static text at baseline and after every 5 hours of training. Reading training consisted of freely chosen leftward scrolling text that could be adjusted in speed and color. The rationale of the therapy was to induce involuntary saccades into the patient's blind right hemifield as a strategy to improve reading when returning to normal, static text. With this paradigm, the authors could demonstrate a significant, training-dependent improvement of reading speeds of up to 46% after 20 hours of training. The free website provides a promising approach to deliver reading training to the home of patients when rehabilitation resources are scarce.

Predicting consciousness recovery in acute patients with vegetative state (VS) is a diagnostic challenge on intensive care units (ICU). Weiss et al. investigated the prognostic value of caloric bedside irrigation in 26 brain-injured patients with VS [5]. They found that the presence of quick phases (rather than slow phases) of caloric nystagmus has a very high positive predictive value of 0.93 for regaining consciousness in these patients. The authors explain the good correlation with the close anatomical relation between the pathways of the

1 vestibulo-ocular reflex and consciousness in the brainstem. This indicator of a favorable
2 outcome may be very helpful for guiding therapeutic decisions on ICU. In another study,
3 Trojano et al. explored the visual tracking behavior of chronic patients with disorders of
4 consciousness [6]. Their goal was to distinguish patients with VS from patients with
5 minimally conscious state, who have a more favorable outcome. The authors found that
6 patients with minimally conscious state fixated significantly more on presented targets, while
7 fixation in patients with VS was at chance level. Quantitative analysis of visual tracking
8 behavior, as proposed by the authors, may therefore be a promising tool for assessing and
9 following up patients with impaired consciousness.
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12 Fatigue is one of the most common symptoms of multiple sclerosis (MS) with a substantial
13 impact on the quality of life of patients. Fatigue is usually assessed with the fatigue severity
14 scale (FSS), but objective measures of fatigue are lacking. Finke et al. set out to quantify
15 fatigue in MS patients with a saccadic fatigue task [7]. They asked MS patients with and
16 without fatigue to continuously perform saccades over a period of 10 minutes. They found
17 that patients with fatigue had a significantly larger decrease of saccade peak velocity and
18 amplitude than patients without fatigue. For their study they used a portable infrared eye-
19 movement recording device, which would allow for convenient bedside testing of fatigue in a
20 clinical setting. The system, however, only provides ‘cyclopean’ recordings of the average
21 position of both eyes. As the authors acknowledge, the presence of internuclear
22 ophthalmoplegia (INO), which is a frequent finding in MS, may interfere with the result in
23 these patients.
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29 **Novel myasthenia gravis autoantibodies**

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31 Ocular myasthenia gravis (MG) is often a diagnostic dilemma, because autoantibodies to
32 acetylcholine receptors (AChR) are negative in over 50% of cases, repetitive nerve
33 stimulation of peripheral muscles has a poor sensitivity, and single fiber electromyography as
34 the current gold standard is cumbersome and uncomfortable for the patients. For these
35 reasons, detection of additional autoantibodies would be very helpful in bridging the
36 diagnostic gap of hitherto ‘seronegative’ ocular MG.
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40 Recently, novel autoantibodies to Kv1.4 have been identified [8]. Kv1.4 is a subunit of the
41 voltage-gated potassium channel (VGKC) involved in the presynaptic release of
42 acetylcholine. The study has been done in a Japanese population, where the antibodies were
43 associated with severe MG with bulbar involvement, myasthenic crisis, thymoma,
44 myocarditis, and QT prolongation on electrocardiogram. Based on this study, Romi et al. set
45 out to investigate the clinical features and serological associations of anti-Kv1.4 antibodies in
46 a Caucasian MG population [9]. They included samples from 129 myasthenia gravis patients
47 with mainly ocular symptoms. They could detect anti-Kv1.4 antibodies in 17% of their
48 patients, most of them women with late-onset MG. So, while in a Japanese population, anti-
49 Kv1.4 autoantibodies seem to be associated with severe MG and thymoma, in Caucasians the
50 same antibodies are associated with mild, late-onset MG in women. To reconcile this
51 disparity, the authors point out to the genetic differences between the two study populations
52 as a likely explanation.
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57 Approximately 10% of patients with generalized MG have neither antibodies against AChR
58 nor muscle-specific tyrosine kinase (MuSK). However, onset and progression of these so-
59 called double-seronegative patients is very similar to seropositive patients. As they respond
60 similarly to plasma exchange and immunosuppressive therapy, the disease is likely caused by
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another pathogenic autoantibody. Recently, autoantibodies to low-density lipoprotein receptor-related protein 4 (Lrp4) have been characterized in patients with AChR-negative MG [10]. In this Japanese population, anti-Lrp4 antibodies have been detected in only 9 out of 300 MG patients. Based on this study, Pevzner et al. analyzed sera from 13 double-seronegative MG patients in a Caucasian population [11]. In contrast to the previous study, they detected autoantibodies against Lrp4 much more frequently in about 50% of their patients (7/13) with a female preponderance and rather late onset. Similar to the differences found for the anti-Kv1.4 antibodies described above, the authors attributed the variation to the different ethnical background of their patients.

In contrast to double-seronegative MG patients, double-seropositive patients are exceedingly rare with only a handful patients reported to date. Rajakulendran et al. described an interesting case with clinically biphasic MG with both AChR and MuSK antibodies [12]. The patient first presented during adolescence with bulbar predilection typical for AChR-positive MG. Following thymectomy she went into complete remission. 15 years later, she presented again, this time with severe oculobulbar, neck and respiratory muscle involvement. She then had several relapses that had to be treated with intravenous immunoglobulins and plasma exchange. At this stage, the patient was tested positive for both AChR and MuSK antibodies. Although the authors could not prove that the patient was MuSK-negative at initial presentation (as it was not tested), they conjecture from the biphasic clinical course that she switched from a predominantly AChR-mediated to a MuSK-mediated phenotype after thymectomy. Based on their experience, the authors recommend testing for MuSK antibodies in MG patients who relapse after thymectomy as this may substantially change their therapeutical approach.

Neuromyelitis optica (NMO) and chronic relapsing inflammatory optic neuropathy (CRION)

Neuromyelitis optica (NMO) is a rare inflammatory and demyelinating disease characterized by optic neuritis and longitudinally extensive transverse myelitis. Eugène Devic and his student Fernand Gault coined the term NMO in 1894 based on 16 patients with this rare association of symptoms [13]. However, Jarius et al. re-discovered an earlier, forgotten report from 1804 by the French pathologist and first physician to Louis XVIII, Antoine Portal (1742–1832), who described a patient with visual loss and spinal cord inflammation but no brain pathology [14]. In another paper, Jarius et al. also highlighted the seminal role of Sir Thomas Clifford Allbutt (1836-1925), best known as the inventor of the clinical thermometer, in piecing the NMO syndrome together based on three cases with the same concurrence of symptoms published in 1870 [15].

As NMO is a rare disease, reliable epidemiological data has been quite sparse. Previous studies in different ethnic groups reported variable prevalence rates between 3.2 (Japan) and 44/million (Denmark). Jacob et al. established the epidemiology of NMO in Merseyside, which is a metropolitan county in North West England with the City of Liverpool as its headquarters [16]. The adult population of Merseyside is about 1.1 million with 94.8% Caucasians, which is approximately representative for the United Kingdom in general. Based on multiple overlapping data sources including hospital records, central anti-aquaporin 4 (AQP4) antibody testing laboratory data and the British Neurological Surveillance Unit, they identified eight cases with NMO or NMO spectrum disorder indicating a prevalence of 7.2/million with an average annual incidence rate of 0.8/million. Extrapolating to the whole UK population, the estimated prevalence would correspond to 365 cases with an average

1 annual incidence rate of 39 cases. The authors point out that the relatively low prevalence
2 compared to other studies probably reflects genetic differences in the population studied.
3 Although the authors took great care in avoiding any ascertainment bias by using overlapping
4 data sources, they admit that some NMO cases may have been missed mainly because of
5 misdiagnosis as multiple sclerosis (MS). Due to increasing awareness of NMO and its varied
6 spectrum, the authors expect the prevalence to rise in the future.
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8 To elucidate the time course of NMO, Uzawa et al. retrospectively analyzed a Japanese cohort
9 of 43 patients with a mean disease duration of 14.2 years [17]. Myelitis and optic neuritis
10 were about equally frequent as initial inflammatory events (44.2% and 41.9%), while both
11 together occurred in about 9.3%. Interestingly, myelitis was found to be the more frequent
12 initial symptom in older patients (>50 years), whereas optic neuritis was seen more often in
13 younger patients (<50 years). By the end of the observation period, 93% of the patients had
14 positive anti-AQP4 antibody titers. The median interval from onset until fulfillment of the
15 2006 NMO criteria [18] was 28 months, indicating the difficulty for early diagnosis of the
16 disease. Based on this diagnostic delay of over 2 years, the authors highlight the need for
17 early diagnostic markers or more specific criteria in order to initiate the appropriate treatment
18 timely.
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23 According to the current diagnostic criteria [18], optic neuritis and myelitis are absolute
24 criteria for NMO. Extension of the myelitis over three or more vertebral segments together
25 with the presence of AQP4 antibodies and a brain MRI that does not meet the criteria for MS
26 further supports the diagnosis of NMO. In a recent study Iorio et al. compared the clinical and
27 neuroimaging characteristics of 37 patients with longitudinally extensive transverse myelitis
28 [19]. 16 of their patients had positive anti-AQP4 antibodies with a higher female to male ratio
29 than the negative patients. In these patients the myelitis was often accompanied by intractable
30 nausea, vomiting and paroxysmal tonic spasms. This was explained by the fact that the
31 inflammatory lesions extended into the brainstem more frequently involving the central grey
32 matter. These distinctive clinical features may help to identify patients with NMO earlier in
33 order to prompt the appropriate treatment.
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38 Despite many similarities with MS, the treatment of NMO is different. Since randomized
39 controlled trials for the treatment of this rare disease are lacking, current therapeutic concepts
40 are still based on expert opinion and consensus criteria [20]. While current best practice
41 recommends oral treatment with azathioprine in combination with corticosteroids, the
42 efficacy of cyclosporine A has not yet been evaluated in NMO. Kageyama et al. reviewed the
43 clinical records of 52 patients with NMO spectrum disorders and included 22 patients for
44 analysis of their treatment [21]. First, the authors confirmed the efficacy of azathioprine in
45 combination with corticosteroids as a treatment for NMO. Second, they provided the first
46 evidence that the combination of cyclosporine A and corticosteroids may be equally effective.
47 Under treatment with cyclosporine A, they observed a significant reduction in the annual
48 relapse rate as well as a decreased dose of concomitantly administered corticosteroids. In
49 summary, the case series provides the first retrospective evidence for the efficacy of
50 cyclosporine A in the treatment of NMO spectrum disorders, but randomized controlled
51 treatment trials are warranted to confirm these results.
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56 In a case report, Juryńczyk et al. reported the deleterious effect of natalizumab in a patient
57 with initially unrecognized NMO [22]. The woman was diagnosed with MS at the age of 22.
58 She had recurrent relapses of spastic paraparesis, sensory deficits and severe right optic
59 neuritis. Over the years, she was treated with interferon β -1a, glatiramer acetate and
60 mitoxantrone. While she was in a stable condition, she was then started on natalizumab. Six
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1 days after the fourth infusion, she suddenly developed a severe relapse with confusion,
2 vomiting and paralysis of her left upper limb. Her brain MRI showed an extensive, non-
3 contrast-enhancing T2-hyperintense lesion. Negative JC virus PCR ruled out progressive
4 multifocal leucoencephalopathy. Based on the presence of anti-AQP4 antibodies, the patient
5 was finally diagnosed with NMO according to the current criteria. Treatment with
6 plasmapheresis and intravenous methylprednisolone led to clinical improvement with
7 resolution of confusion after two weeks. In line with previous reports, this clinical case
8 highlights that, following a few infusions, natalizumab may induce a severe relapse in patients
9 with NMO. The authors therefore recommend testing for anti-AQP4 antibodies in atypical
10 MS patients, especially with severe spinal and/or optic nerve involvement, before natalizumab
11 initiation and in patients who develop extensive brain lesions during treatment.
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14 Horwitz et al investigated the diagnostic value of a lumbar puncture in patients with optic
15 neuritis depending on the result of visual evoked potential (VEP) and MRI examination of the
16 brain [23]. For this purpose, they retrospectively analyzed 437 patients who presented with
17 optic neuritis without known MS prior to referral. They found that cerebrospinal fluid (CSF)
18 abnormalities (elevated leucocytes, elevated IgG index or oligoclonal bands) correlated
19 strongly with pathological VEP and MRI results ($p < 0.0001$). Vice versa, they calculated that
20 patients with both normal MRI and VEP had a 96 % probability of normal CSF findings.
21 From their results they concluded that the diagnostic contribution of a lumbar puncture to the
22 evaluation of optic neuritis is negligible in patients with normal VEP and MRI. Therefore, the
23 authors suggested that all patients with suspected optic neuritis should be evaluated with VEP
24 and MRI before deciding on a lumbar puncture.
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29 Apart from NMO, the differential diagnosis of optic neuritis includes the rare entity of
30 chronic relapsing inflammatory optic neuropathy (CRION), which was first described by
31 Kidd et al. in 2003 [24]. In a systematic literature review, Petzold et al. now analyzed 122
32 patients with CRION over the last decade [25]. They characterized it as a rare, worldwide
33 disease with a peak in the fourth decade and a female preponderance. Typically, patients
34 presented with bilateral simultaneous or sequential, mostly severe visual loss and at least one
35 relapse. Pain at onset was reported in at least about a third of the cases and particularly
36 recurrence of pain after reducing or stopping the steroids was noted as a red flag. Importantly,
37 most of the patients were negative for AQP4 antibodies, suggesting that CRION is an entity
38 distinct from NMO. In addition, MRI scans of the brain did not show demyelinating lesions
39 typical for MS. Taken together, its etiology still remains unknown, but seems likely to be
40 immune-mediated. All patients treated with methylprednisolone responded, but relapsed after
41 stopping the treatment. Therefore, oral steroids had to be carefully tapered under rigorous
42 follow-up to identify the individual minimal effective dose. As a consequence of the steroid-
43 dependency, steroid-sparing agents (azathioprine, methotrexate, cyclophosphamide or
44 mycophenolate) had to be used in many cases. But as a silver lining, in the experience of the
45 authors, disease activity sometimes settled over a decade. Based on their careful review with
46 the key points outlined above, they proposed revised diagnostic criteria for CRION (table 1).
47 Since the diagnosis of CRION based on these criteria remains mainly clinical without any
48 specific blood biomarker, the authors hope for the discovery of a novel antibody, which
49 would facilitate early diagnosis and adequate treatment of the disease.
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Cerebellar downbeat nystagmus: treatment with 4-aminopyridine

Hypofunction of the cerebellar flocculus causes - among other ocular motor signs - downbeat nystagmus (DBN) that, in turn, may lead to debilitating vertical oscillopsia. In recent years, 4-aminopyridine (4AP), a potassium channel blocker that increases Purkinje cell excitability, has become a valuable therapeutic option to dampen cerebellar DBN. 4AP also prevents attacks in episodic ataxia type 2 and improves cerebellar gait disorders. Fampridine is the sustained-release form of 4AP. Only two doses per day are required and cardiac side effects (prolonged QTc-time) are less common than in 4AP. Fampridine is usually well tolerated by patients [26].

In patients with ataxia-telangiectasia (A-T), which typically involves the cerebellum, Shaikh et al. studied the effect of 4AP on ocular motor signs [27]. 4AP reduced deficits ascribed to the loss of cerebellar Purkinje cells in these patients. Specifically, 4AP shortened the time constant of the horizontal vestibulo-ocular reflex and decreased spontaneous and periodic alternating nystagmus.

In a patient with a right posterior vermis lesion leading to positional DBN and vertigo, 4AP was beneficial [28]. The lesion had caused hypofunction of the nodulus and flocculus/paraflocculus, as demonstrated with FDG-PET. This hypofunction was partly reversed by 4AP, which suggests that the cerebellar structures inhibiting the upward ocular drift bias were functionally restored by the substance.

Another patient with a cerebellar ocular motor syndrome showed a reversal of DBN into upbeat nystagmus (UBN) after a test dose of fampridine [29]. Most likely, fampridine caused a transient over-activity of Purkinje cell neurons in this patient. This, in turn, increased the inhibition of superior vestibular nuclei neurons, which predominantly encode in the upward direction. Consequently, the eyes drifted downward leading to UBN.

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Highlights [box with bullet points]

- *Read-Right*, a free web-based application (www.readright.ucl.ac.uk) improves reading in patients with right-sided hemianopia [4].
- The presence of nystagmus fast phases after caloric irrigation predicts consciousness recovery in patients with vegetative state on ICU [5].
- Anti-Kv1.4 [9] and anti-Lrp4 [11] are promising novel autoantibodies for the diagnosis of hitherto ‘seronegative’ myasthenia gravis.
- While cyclosporine A may be effective in the treatment of NMO [21], natalizumab may have deleterious effects [22].
- 4-aminopyridine (4AP) and fampridine (sustained-release form of 4AP) are effective treatments of spontaneous and positional downbeat nystagmus resulting from vestibulo-cerebellar hypofunction [26,27].

Table 1

Revised diagnostic criteria for chronic relapsing inflammatory optic neuropathy (CRION)
[25]

1. *History*: optic neuritis and at least one relapse.
2. *Clinical*: Objective evidence for loss of visual function.
3. *Labor*: NMO-IgG seronegative.
4. *Imaging*: Contrast enhancement of the acutely inflamed optic nerves (optic nerve atrophy at later stages).
5. *Treatment*: Response to immunosuppressive treatment and relapse on withdrawal or dose reduction.

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